UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/907,041	08/06/1997	JOEL S. GREENBERGER	76333/103	7766

7590 10/08/2002

FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 200075109

EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	20

DATE MAILED: 10/08/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/907,041	Joel S. Greenberger
Examiner	**Art Unit**
Shin-Lin Chen	1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on Jul 24, 2002

2a) [ ] This action is **FINAL.** 2b) [X] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) 1-33 is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) 1-32 is/are rejected.

7) [X] Claim(s) 33 is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirem

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are a) [ ] accepted or b) [ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved by the Examiner

If approved, corrected drawings are required in reply to this Office action.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) [ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) [ ] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____ .
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) [ ] The translation of the foreign language provisional application has been received.

15) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [X] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
4) [ ] Interview Summary (PTO-413) Paper No(s). _____
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other

DETAILED ACTION

Applicant's amendment and terminal disclaimer filed 7-24-02 have been entered. Claims 32 and 33 have been added. Claims 1-33 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for radiation-resistant of murine melanoma cell line B16 via higher expression of γ-GTP, expression of a MnSOD transgene under control of the irradiation inducible egr-1 promoter that increases the radioresistance of 32D CL 3 hematopoietic progenitor cells *in vitro*, and protection of cells of target site from irradiation via administration of polynucleotide encoding MnSOD, MT, or gamma-GTP to a subject locally to said targeted site, does not reasonably provide enablement for a method for protecting a subject against any agent that produces toxic species including free radicals, superoxide anions, and heavy metals, by administering a pharmaceutical composition, comprising a polynucleotide or any vector encoding a protein that is capable of neutralizing or eliminating said toxic species, to said subject **via systemic administration routes** to protect any targeted site *in vivo* or protecting cells from agents that elicit toxic species that are remote from the administration site of said pharmaceutical

composition, and said pharmaceutical composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-32 are directed to a method for protecting a subject against an agent that elicits free radicals, superoxide anions, or heavy metal cations, said method comprising the steps of administering to said subject *in vivo* a pharmaceutical composition comprising a polynucleotide that encodes a protein transiently expressed in said subject, and a pharmaceutically acceptable vehicle for said polynucleotide; and a pharmaceutical composition comprising said polynucleotide in a pharmaceutically acceptable vehicle. Claim 32 specifies the administration is intratracheal injection.

The specification discloses the construction of recombinant adenoviral vectors Ad-MT, Ad-MnSOD, and Ad-γ-GTP; the expression of metallothionein (MT), manganese superoxide dismutase (MnSOD), and γ-Glutamyltranspeptidase (γ-GTP) in rat lung epithelium *in vivo*, and the function assay for MT, MnSOD, and γ-GTP proteins. The specification discloses expression of greater levels of γ-GTP in murine melanoma cell line B16 renders the cell line less sensitive to γ-irradiation, and expression of a MnSOD transgene under control of the irradiation inducible egr-1 promoter increases the radioresistance of 32D CL 3 hematopoietic progenitor cells *in vitro*.

The claims encompass protecting a subject from an agent producing toxic species by administering a pharmaceutical composition comprising a polynucleotide encoding a protein that is able to neutralize said toxic species via **any administration routes** *in vivo* and protecting any

cell in a subject by intratracheal injection of said pharmaceutical composition. The post-filing evidence provided in the reply submitted 3-20-02 only discloses protection of cells of a target site from radiation via local administration to said target site of a polynucleotide encoding MnSOD, such as intratracheal injection, intraesophageal injection, or direct injection into small intestine. The specification fails to provide adequate guidance and evidence that systemic administration of a polynucleotide encoding a protein capable of neutralizing toxic species can protect cells at any particular target site in a subject *in vivo*. The specification fails to provide adequate guidance and evidence that administration of a pharmaceutical composition containing any vector comprising a polynucleotide encoding a protein capable of neutralizing toxic species to a site that is very remote from the site to be treated with irradiation can protect cells in any site to be protected from irradiation other than the administration site of said pharmaceutical composition in a subject *in vivo*. The specification also fails to provide adequate guidance and evidence that intratracheal administration of the pharmaceutical composition set forth above can protect cells other than the cells of administration site, i.e. palmonary cells, from irradiation *in vivo*.

The phrase "pharmaceutical composition" in claims 27-29 implies therapeutic effect *in vivo*. Thus, claims 1-32 read on gene therapy *in vivo*. The state of the art for gene therapy was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems

hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Different vectors has different gene transfer efficiency and the specification fails to provide adequate guidance and evidence that systemic administration of a pharmaceutical composition containing various vector can protect cells of any target site from agents that elicit toxic species in a subject.

Further, Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA are all important factors for a successful gene therapy (e.g. bridging pages 81-82). There is no evidence of record that administration of a pharmaceutical

composition containing a polynucleotide or any vector encoding a protein capable of neutralizing toxic species via any systemic administration route could protect cells of any target site from agents that elicit toxic species in a subject. There is no evidence of record that delivery of a pharmaceutical composition containing a polynucleotide or any vector encoding a protein capable of neutralizing toxic species to a subject via intratracheal administration can protect cells, which are remote from the administration site, from irradiation in a subject *in vivo*. One skilled in the art would not know how to use the claimed pharmaceutical composition to practice over the full scope of the invention claimed.

For the reasons discussed above, it would require undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Applicant cites the reference submitted 7-24-02 and argues that the present invention is protective *in vivo* and is not clear whether the rejection of the scope of the polynucleotide vectors is maintained (amendment, p. 2-3). This is not found persuasive because of the reasons set forth above and that the cited references only teach **intratracheal injection** of a vector expressing MnSOD can protect **lung cells**. The cited references fail to provide enabling disclosure that administration of a pharmaceutical composition containing a polynucleotide or **any vector** encoding a protein capable of neutralizing toxic species via any **systemic administration** route

could protect cells of any target site from agents that elicit toxic species in a subject. There is no evidence of record that delivery of a pharmaceutical composition containing a polynucleotide or any vector encoding a protein capable of neutralizing toxic species to a subject via intratracheal administration can protect cells, which are remote from the administration site, from irradiation in a subject *in vivo*.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 27 and 28 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Branch et al., 1993 (American Review of Respiratory Disease, Vol. 147(4): supp. S, pp. A206).

Claims 27 and 28 are directed to a pharmaceutical composition comprising a polynucleotide that encodes a protein that is capable of neutralizing or eliminating toxic species, such as a free radical, a superoxide anion, or a heavy metal, and a pharmaceutically acceptable vehicle for said polynucleotide. Claim 28 specifies the polynucleotide encodes a gamma glutamyl transpeptidase (gamma-GTP), a manganese superoxide dismutase (Mn-SOD), or a metallothionein (MT).

Branch teaches transfection of BPAEC cells with human MnSOD cDNA that was inserted into a pCMV plasmid. The buffer solution containing the plasmid expressing human MnSOD is considered a pharmaceutically acceptable vehicle. Thus, claims 27 and 28 are anticipated by Branch.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 27 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Branch et al., 1993 (American Review of Respiratory Disease, Vol. 147(4): supp. S, pp. A206) in view of Nabel et al., 1994 (Anals New York Academy of Sciences, Vol. 714, p. 247-252).

Claims 27 and 29 are directed to a pharmaceutical composition comprising a polynucleotide that encodes a protein that is capable of neutralizing or eliminating toxic species, such as a free radical, a superoxide anion, or a heavy metal, and a pharmaceutically acceptable vehicle for said polynucleotide. Claim 29 specifies the pharmaceutically acceptable vehicle is a liposome, an adenovirus vector, or a ligand-DNA conjugate.

Branch teaches transfection of BPAEC cells with human MnSOD cDNA that was inserted into a pCMV plasmid. The buffer solution containing the plasmid expressing human MnSOD is considered a pharmaceutically acceptable vehicle.

Branch does not teach using adenovirus vector or liposome as a pharmaceutically vehicle.

Nabel teaches using retrovirus, adenovirus, adenoviral conjugates, and cationic liposomes for delivery of foreign DNA into vascular cells *in vitro* and *in vivo* (e.g. p. 247). Nabel teaches the use of those vectors for gene delivery in gene therapy *in vivo*.

It would have been obvious for one of ordinary skill at the time of the invention to substitute the plasmid as taught by Branch with adenovirus vector or liposome as taught by Nabel in order to introduce the human MnSOD into target cells, such as vascular cell, and for gene delivery in gene therapy as taught by Nabel with reasonable expectation of success.

It should be noted that the term "pharmaceutical" does not carry weight in 102(b) or 103(a) rejection.

Conclusion

7. Claims 1-32 are rejected. Claim 33 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Scott Priebe can be reached on (703) 308-7310. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.